

the Wnt and Dpp/BMP families of morphogens, proteins which impart positional information. In development of the CNS and patterning of limbs in vertebrates, the introduction of *hedgehog*

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

Please cancel claim 8, without prejudice.

sub E1
D3
1. (Amended) A method for inhibiting degradation in functional performance of motor or sensory nerves in an animal comprising systemically administering to the animal an amount of a *hedgehog* agonist sufficient to inhibit degradation in the functional performance of motor or sensory nerves.

2. (Amended) A method for inhibiting dysfunction of motor or sensory nerve cells in a patient comprising systemically administering to the patient an amount of a *hedgehog* agonist effective to inhibit dysfunction of motor or sensory nerve cells.

sub E2
3. (Twice Amended) A method for the treatment or prophylaxis of peripheral neuropathy comprising systemically administering to an animal an amount of a *hedgehog* agonist sufficient to treat or prophylactically treat peripheral neuropathy.

4. (Twice Amended) A method for protecting peripheral nerve cells under conditions which otherwise result in peripheral neuropathy, comprising systemically administering to a patient in need thereof an effective amount of a *hedgehog* agonist sufficient to protect peripheral nerve cells from peripheral neuropathy.

sub E3
5. (Amended) A method for the treatment or prophylaxis of diabetic neuropathy comprising systemically administering to a patient in need thereof an effective amount of a *hedgehog* agonist sufficient to treat or prophylactically treat diabetic neuropathy.

sub E3
cont.
D5

6. (Amended) A method for the treatment or prophylaxis of virally induced peripheral neuropathy comprising systemically administering to a patient in need thereof an effective amount of a *hedgehog* agonist sufficient to treat or prophylactically treat virally induced peripheral neuropathy.

7. (Amended) The method of any of claims 1-6, wherein the *hedgehog* agonist is a polypeptide which includes a *hedgehog* amino acid sequence at least 80 percent identical to at least one of SEQ ID Nos. 10-18 or any fragment thereof that binds to a *patched* polypeptide.

sub E4
D6

9. (Amended) The method of claim 7, wherein the *hedgehog* amino acid sequence is at least 90 percent identical to at least one of SEQ ID Nos. 10-18 or any fragment thereof that binds to a *patched* polypeptide.

10. (Amended) The method of claim 7, wherein the *hedgehog* amino acid sequence is encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2X SSC at 65 °C, to at least one of SEQ ID Nos. 1-9.

11. (Amended) The method of claim 7, wherein the *hedgehog* amino acid sequence is a vertebrate *hedgehog* polypeptide.

sub E5
D7

13. (Amended) The method of claim 7, wherein the polypeptide includes at least a 50 amino acid extracellular portion of a vertebrate *hedgehog* polypeptide selected from at least one of SEQ ID Nos. 10-18.

14. (Amended) The method of claim 7, wherein the polypeptide includes at least a 150 amino acid extracellular portion of a vertebrate *hedgehog* polypeptide selected from at least one of SEQ ID Nos. 10-18.

15. (Amended) The method of claim 7, wherein the polypeptide includes at least an extracellular portion of a vertebrate *hedgehog* polypeptide corresponding to residues 24-194 of SEQ ID No:15.

sub E5
cont.

16. (~~Amended~~) The method of claim 7, wherein the polypeptide is modified with one or more lipophilic moieties.

D7
cont

17. (~~Amended~~) The method of claim 16, wherein the polypeptide is modified with one or more sterol moieties.

18. (~~Reiterated~~) The method of claim 17, wherein the sterol moiety is cholesterol.

19. (~~Amended~~) The method of claim 16, wherein the polypeptide is modified with one or more fatty acid moieties.

D8

20. (~~Amended~~) The method of claim 19, wherein each fatty acid moiety is independently selected from myristoyl, palmitoyl, stearoyl, or arachidoyl.

21. (~~Amended~~) The method of claim 16, wherein the polypeptide is modified with one or more aromatic hydrocarbons.

D9

22. (~~Twice Amended~~) The method of claim 21, wherein each aromatic hydrocarbon is independently selected from benzene, perylene, phenanthrene, anthracene, naphthalene, pyrene, chrysene, or naphthacene.

D10

23. (~~Amended~~) The method of claim 16, wherein the polypeptide is modified one or more times with a C7 - C30 alkyl or cycloalkyl.

D11

30. (~~Amended~~) The method of any of claims 1-6, wherein the *hedgehog* agonist mimics *hedgehog* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in *hedgehog* signaling.

31. (~~Amended~~) The method of any of claims 1-6, wherein the *hedgehog* agonist alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in *hedgehog* signal transduction.

D12 41. (Amended) The method of any of claims 4-6, wherein the patient is being treated prophylactically.

D13 44. (Twice Amended) The method of claim 4, 5, or 6, which method is part of a protocol for the treatment of an acquired neuropathy.

45. (Amended) The method of claim 44, wherein the neuropathy is due to viral infection, diabetes or inflammation.

46. (Reiterated) The method of claim 44, wherein the neuropathy is due to contact with a toxic agent.

D14 47. (Amended) The method of claim 44, wherein the neuropathy is selected from diabetic neuropathy; immune-mediated neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic polyneuropathy with antibodies to peripheral nerves, neuropathies associated with vasculitis or inflammation of the blood vessels in peripheral nerve, brachial or lumbosacral plexitis, and neuropathies associated with monoclonal gammopathies; neuropathies associated with tumors or neoplasms such as sensory neuropathy associated with lung cancer, neuropathy associated with multiple myeloma, neuropathy associated with waldenstrom's macroglobulemia, chronic lymphocytic leukemia, or B-cell lymphoma; neuropathy associated with amyloidosis; neuropathies caused by infections; neuropathies caused by nutritional imbalance; neuropathy in kidney disease; hypothyroid neuropathy; neuropathy caused by alcohol and toxins; neuropathies caused by drugs; neuropathy resulting from local irradiation; neuropathies caused by trauma or compression; or idiopathic neuropathies.

48. (Amended) The method of claim 4, 5, or 6, which method is part of a protocol for the treatment of a hereditary neuropathy.

50. (Amended) The method of claim 4, 5, or 6, which method is part of a protocol for slowing neurodegenerative events associated with age-related neuropathology.

D15
sub E67 51. (Amended) ~~IE~~ The method of claim 7, wherein the polypeptide is a fusion protein.

Please add the following new claims:

52. The method of claim 7, wherein the *hedgehog* amino acid sequence is at least 95 percent identical to at least one of SEQ ID Nos. 10-18 or any fragment thereof that binds to a *patched* polypeptide.

53. The method of claim 7, wherein the *hedgehog* amino acid sequence is identical to at least one of SEQ ID Nos. 10-18 or any fragment thereof that binds to a *patched* polypeptide.

54. The method of claim 7, wherein the fragments are N-terminal fragments.

55. The method of claim 54, wherein the N-terminal fragments have a molecular weight of about 19 kD.

56. The method of claim 7, wherein the polypeptide is modified with one or more lipophilic amino acid residues or lipophilic peptides.

57. The method of claim 56, wherein the polypeptide is modified at the N-terminus by the one or more amino acid residues or peptides.

58. The method of claim 16, wherein the polypeptide is modified at the N-terminus by the one or more lipophilic moieties.

The amended claims are re-stated below to reflect changes with respect to the last filing.

1. (Amended) A method for [preventing] inhibiting degradation in functional performance of motor or sensory nerves in an animal comprising systemically administering to the animal [a therapeutic] an amount of a *hedgehog* agonist sufficient to inhibit degradation in the functional performance of motor or sensory nerves [or *ptc* therapeutic].

2. (Amended) A method for [preventing] inhibiting dysfunction of motor or sensory nerve cells in a patient comprising systemically administering to the patient [contacting the cells with] an [effective] amount of a hedgehog agonist effective to inhibit dysfunction of motor or sensory nerve cells [or *ptc* therapeutic].
3. (Twice Amended) A method for [treating or preventing] the treatment or prophylaxis of peripheral neuropathy comprising systemically administering to an animal [a protective] an amount of a hedgehog agonist sufficient to treat or prophylactically treat peripheral neuropathy [or *ptc* therapeutic].
4. (Twice Amended) A method for protecting peripheral nerve cells under conditions which otherwise result in peripheral neuropathy, comprising systemically administering to a patient in need thereof [a therapeutically] an effective amount of a hedgehog agonist sufficient to protect peripheral nerve cells from peripheral neuropathy [or *ptc* therapeutic].
5. (Amended) A method for the [treating or preventing] treatment or prophylaxis of diabetic neuropathy comprising systemically administering to a patient in need thereof [a therapeutically] an effective amount of a hedgehog agonist sufficient to treat or prophylactically treat diabetic neuropathy [or *ptc* therapeutic].
6. (Amended) A method for the [treating or preventing] treatment or prophylaxis of virally]-induced peripheral neuropathy comprising systemically administering to a patient in need thereof [a therapeutically] an effective amount of a hedgehog agonist sufficient to treat or prophylactically treat virally induced peripheral neuropathy [or *ptc* therapeutic].
7. (Amended) The method of any of claims 1-6, wherein the hedgehog agonist [therapeutic] is a polypeptide which includes a hedgehog amino acid sequence [which is] at least 80 percent identical [or homologous to an amino acid sequence of any one] to at least one of SEQ ID Nos. 10-18 or any fragment thereof that binds to a patched polypeptide.

9. (Amended) The method of claim 7, wherein the *hedgehog* amino acid sequence is at least [80]90 percent identical to [an amino acid sequence of any one]at least one of SEQ ID Nos. 10-18 or any fragment thereof that binds to a patched polypeptide.
10. (Amended) The method of claim 7, wherein the *hedgehog* amino acid sequence is encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2X SSC at 65 °C, to [any one]at least one of SEQ ID Nos. 1-9.
11. (Amended) The method of claim 7, wherein the *hedgehog* amino acid sequence is [of] a vertebrate *hedgehog* polypeptide [protein].
13. (Amended) The method of claim 7, wherein the polypeptide includes at least a 50 amino acid extracellular portion of a vertebrate *hedgehog* [protein]polypeptide selected from at least one of SEQ ID Nos. 10-18.
14. (Amended) The method of claim 7, wherein the polypeptide includes at least a 150 amino acid extracellular portion of a vertebrate *hedgehog* [protein]polypeptide selected from at least one of SEQ ID Nos. 10-18.
15. (Amended) The method of claim 7, wherein the polypeptide includes at least an extracellular portion of a vertebrate *hedgehog* [protein]polypeptide corresponding to residues 24-194 of SEQ ID No:15.
16. (Amended) The method of claim 7, wherein the [hedgehog] polypeptide is modified with one or more lipophilic moieties.
17. (Amended) The method of claim 16, wherein the [hedgehog] polypeptide is modified with one or more sterol moieties.
19. (Amended) The method of claim 16, wherein the [hedgehog] polypeptide is modified with one or more fatty acid moieties.

20. (Amended) The method of claim 19, wherein each fatty acid moiety is independently selected from [the group consisting of] myristoyl, palmitoyl, stearoyl, [and]or arachidoyl.
21. (Amended) The method of claim 16, wherein the [hedgehog] polypeptide is modified with one or more aromatic hydrocarbons.
22. (Twice Amended) The method of claim 21, wherein each aromatic hydrocarbon is independently selected from [the group consisting of] benzene, perylene, phenanthrene, anthracene, naphthalene, pyrene, chrysene, [and]or naphthacene.
23. (Amended) The method of claim 16, wherein the [hedgehog] polypeptide is modified one or more times with a C7 - C30 alkyl or cycloalkyl.
30. (Amended) The method of any of claims 1-6, wherein the [*ptc* therapeutic]hedgehog agonist mimics *hedgehog*[-mediated *patched*] signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in *hedgehog* signaling [a *patched* signal pathway].
31. (Amended) The method of any of claims 1-6, wherein the [*ptc* therapeutic] hedgehog agonist alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in [the intracellular] hedgehog signal transduction [pathway of *patched*].
41. (Amended) The method of any of claims 4-6, wherein the patient is being treated prophylactically.
44. (Twice Amended) The method of claim 4, 5, or 6 [or 43], which method is part of a protocol for the treatment of an acquired neuropathy.
45. (Amended) The method of claim 44, wherein the neuropathy is due to viral infection, diabetes or [inflammation]inflammation.

47. **(Amended)** The method of claim 44, wherein the neuropathy is selected from [the group consisting of] diabetic neuropathy; immune-mediated neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic polyneuropathy with antibodies to peripheral nerves, neuropathies associated with vasculitis or inflammation of the blood vessels in peripheral nerve, brachial or lumbosacral plexitis, and neuropathies associated with monoclonal gammopathies; neuropathies associated with tumors or neoplasms such as sensory neuropathy associated with lung cancer, neuropathy associated with multiple myeloma, neuropathy associated with waldenstrom's macroglobulemia, chronic lymphocytic leukemia, or B-cell lymphoma; neuropathy associated with amyloidosis; neuropathies caused by infections; neuropathies caused by nutritional imbalance; neuropathy in kidney disease; hypothyroid neuropathy; neuropathy caused by alcohol and toxins; neuropathies caused by drugs; neuropathy resulting from local irradiation; neuropathies caused by trauma or compression; [and]or idiopathic neuropathies.

48. **(Amended)** The method of claim 4, 5, or 6 [or 43], which method is part of a protocol for the treatment of a hereditary neuropathy.

50. **(Amended)** The method of claim 4, 5, or 6 [or 43], which method is part of a protocol for slowing neurodegenerative events associated with age-related neuropathology.

51. **(Amended)** The method of claim 7, wherein the [hedgehog] polypeptide is a fusion protein.

REMARKS

Claims 1-51 are the pending claims in the present application. Claims 1-11, 13-23, 30, 31, 41, 44-48, 50, and 51 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter. Applicants cancel claim 8, without prejudice. Applicants add new claims 52-58. Support for the subject matter of these claims is found throughout the specification. No new matter has been added. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.